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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,139	NAGATA ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 Feb. 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending in the instant application. Claims 8, 9 and 15 have been amended and claims 16-18 have been added as requested by Applicant in the Paper filed April 13, 2005.

Claims 1-7 and 10-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 8, 9 and 15-18 are currently under examination.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Specification

The objections to the specification are withdrawn in view of Applicants amendment except for the following:

3. The disclosure is objected to because of the following informalities:

Sequences are disclosed in Figures 1-12 without the required reference to the sequence identifiers (SEQ ID NOS:). Also, the instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. On page 24 of the response Applicants state that a Preliminary Amendment was submitted to the USPTO on March 1, 2002, in which the figure descriptions beginning at page

12, line 15 of the specification were amended to insert sequence identifiers. The Examiner has searched the IFW file, but there were no preliminary amendments of record filed March 1, 2002, and a search of all papers filed did not result in any amendments to the figure legends. It is requested that Applicants submit an amendment to insert sequence identifiers.

Applicants are required to amend the specification to comply with

37 C.F.R. §1.821(d).

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8, 9 and 15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using Fas antagonists to treat Graft versus Host Disease (GVHD) that are Fas derived, anti-Fas antibodies or anti-Fas ligand antibodies, does not reasonably provide enablement for using antisense oligonucleotides for the mRNA or the gene of Fas or Fas ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

On pages 26-29 Applicants traverse the rejection and assert that at the time of the invention, the use of antisense oligonucleotides as an in vivo therapeutic agent was well-known to those of ordinary skill in the art, and submit three references which exemplify the use of antisense oligonucleotides as a therapeutic agent. Applicants submit that it was not necessary for

the enablement of the invention for the Applicants to include a detailed description in the specification of how to use anti-sense oligonucleotides. Applicants further note that the prophylactic or therapeutic method of treating graft versus host disease using Fas or Fas ligand antisense oligonucleotides as an active component is not directed to a general method of gene therapy, but rather for a method of using Fas or Fas ligand antisense oligonucleotides, and an example of a sequence of Fas antisense nucleotides that may be used as the active component was described in WO 95/13293, which is incorporated by reference on page 30 of the specification.

Applicants' arguments have been fully considered but are not deemed persuasive. First, the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f). Because the reference is a foreign patent in Japanese, a translation of the document would also be necessary.

Second, the argument that it was not necessary for the enablement of the invention for the Applicants to include a detailed description in the specification of how to use anti-sense oligonucleotides has been fully considered but is not deemed persuasive. The invention is drawn to methods of inhibiting the expression of Fas or Fas ligand *in vivo* as a method of treating

GVHD. The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* is unpredictable. Thus, although the specification prophetically considers using the oligonucleotides *in vivo*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Although Applicants have provided two references in which antisense methodologies were successful, and a third reference which teaches that inhibiting gene expression may be therapeutic (and which also teaches that antisense strategies don't always work), the state of antisense-mediated gene inhibition is highly unpredictable.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially

unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA" (Pg. 4503, para. 1 and 2). Gabler et al. also address this issue, and teach that many researchers use computer programs which make predictions of the secondary structure or the target RNA, and that one of the most frequently used programs is 'mfold'. "However, several reports call the reliability of prediction of accessible and inaccessible sites on mRNAs by 'mfold' into question; thus computer prediction methods alone seem not to be sufficient for designing effective antisense ODNs." (Pgs. 1-2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its

target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the prior art at the time of applicants' filing would not enable antisense therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior

art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification enough to overcome the unpredictability of *in vivo* methods of inhibition, as exemplified in the references above.

The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the antisense administered, and specifically regarding the instant methods claimed.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or prevention GVHD, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate cells and /or tissues such that inhibition is achieved and treatment attained. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. Therefore, the rejection is maintained.

Priority Determination

5. The effective priority date of the instant application is determined to be Oct. 31, 1997, because a translation of the foreign papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8, 9 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 9 and 15-18 are indefinite because claims 8, 15 and 16 encompass a method of treating graft versus host disease comprising administering an effective amount of a Fas antagonist **providing activity to interact with** the extracellular domain of the Fas ligand or the extracellular domain of Fas, and it is not clear what is meant by **providing activity to interact with**. For example, an anti-Fas antibody may bind to the extracellular domain of Fas, but then such binding may be neutral (no effect on Fas) or an antibody may inhibit or stimulate Fas upon binding. The term **providing activity to interact with** does not adequately define what is being claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7.1 Claims 8, 9 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barr et al., U.S. Patent No. 5,652,210, effective priority date Nov. 15, 1993, and further in view of Palmer et al., U.S. Patent No. 5,776,718, priority date March 24, 1995, or Du et al., BBRC, Vol. 226, pages 595-600, Sept. 24, 1996, or Braun et al., J. Exp Med., Vol. 183, pages 657-661, February 1996, or Baker et al., Journal of Experimental Medicine, Vol. 183, June 1996, pages 2645-2656.

Claims 8, 9 and 15-17 encompass a method of treating graft versus host disease (GVHD) comprising administering a Fas antagonist which may be a soluble derivative of Fas (e.g., the extracellular domain, which would bind to Fas ligand and inhibit its interaction with Fas).

Barr et al. disclose a soluble derivative of Fas, and teach that this derivative can be used to treat Fas mediated disorders by binding to the Fas ligand and inhibiting Fas ligand from binding to and activating Fas (column 6, lines 5-24). Barr et al. do not teach that a Fas-mediated disorder is GVHD.

Palmer et al. teach that ICE is involved in the signal transduction of Fas-mediated apoptosis, and that ICE inhibitors may be used in the treatment of graft versus host disease by inhibiting Fas signaling (column 30, line 57 to column 31, line 22).

Du et al. teach that a hammerhead rhibozyme that targets both Fas-ligand and perforin mRNAs, can be used in a method of treating GVHD.

Braun et al. discloses experiments in a mouse GVHD model in which donor cells from Fas-L deficient mice delayed the onset of GVHD versus compared to donor cells that had functional Fas-L (Figure 4a), and teach that the development of therapeutic strategies aimed at controlling this cytolytic pathway (in addition to perforin, which was also shown to be an important mediator of GVHD) during bone marrow transplantation may be an approach for decreasing the risk of GVHD (page 660, last paragraph).

Baker et al. performed experiments in a murine model of GVHD in which donor cells from FasL deficient mice or FasL expressing were transplanted into mice, and the effects compared. Recipients receiving cells from FasL deficient mice had greatly diminished GVHD symptoms, and the authors concluded that Fas-mediated cytotoxicity plays an important role in the pathophysiology of hepatic and cutaneous GVHD after bone marrow transplantation between MHC- matched allogeneic mice (pages 2649-2654).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the soluble Fas of Barr et al. in a method of treating GHVD, since Palmer, Du, Braun and Baker teach or suggest that the Fas pathway is at least partly responsible for some of the effects in GVHD. The skilled artisan would be motivated to do so because of the large number of transplants done and the need to reduce GVHD. There would be a reasonable expectation of success, since a soluble version of Fas would be expected to be an effective inhibitor of the Fas pathway.

7.2 Claims 8, 9 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lynch et al.,. Patent No. 5,620,889, effective priority date Oct. 13, 1994, and further in view of Palmer et al., U.S. Patent No. 5,776,718, priority date March 24, 1995, or Du et al., BBRC, Vol. 226, pages 595-600, Sept. 24, 1996, or Braun et al., J. Exp Med., Vol. 183, pages 657-661, February 1996, or Baker et al., Journal of Experimental Medicine, Vol. 183, June 1996, pages 2645-2656.

Claims 8, 9 and 15-17 encompass a method of treating graft versus host disease (GVHD) comprising administering a Fas antagonist which may be an anti-Fas antibody.

Lynch et al. teach monoclonal antibodies to Fas, and teach that such antibodies can be used therapeutically to inhibit Fas ligand mediated apoptosis of cells (abstract, column 2, lines 18-52. Lynch et al. do not teach that a Fas-mediated disorder is GVHD.

The teachings of Palmer, Du, Braun and Baker are discussed above.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to treat GVHD with the antibodies of Lynch et al., since Lynch et al. demonstrated that the anti-Fas antibodies were effective in inhibiting the Fas mediated

pathway, and Palmer et al., Du et al., Braun et al. and Baker et al. teach that the Fas pathway is involved in GVHD. The skilled artisan would be motivated to do so because the antibodies could be made and purified in large quantities, and Lynch et al. demonstrated that the antibodies were effective in inhibiting the Fas pathway.

Applicants traverse the previous rejection under 35 USC § 103 on pages 31-34 of the response, and assert that there were multiple reports that contradict the reported findings relied upon by the Examiner, and it was not known at the time of the invention whether treating GVHD by targeting the Fas/FasL pathway should be by increasing Fas/FasL-mediated apoptosis or by inhibiting Fas/FasL-mediated apoptosis. Applicants present two references in which functional Fas ligand has a protective effect against graft rejection, and assert that given the unpredictability and controversy in the field at the time of the invention, it would not have been obvious to administer a Fas antagonist to treat GVHD. Applicants' arguments have been fully considered but are not deemed persuasive. Even though there are references that teach away from the claimed invention, there are many references which teach or suggest that GVHD could be treated with an antagonist of the Fas/FasL pathway, and the state of the art as a whole is taken into account. It would have been obvious to one of ordinary skill in the art to try to treat GVHD with an antagonist of the Fas/FasL pathway.

It is believed that all pertinent arguments have been answered.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B O'Hara

EILEEN B. O'HARA
PATENT EXAMINER